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EXPEDITED PUBLICATIONS

A Meta-Analysis of 16 Randomized Trials of Sirolimus-Eluting Stents Versus Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease

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Objectives Our purpose was to make a synthesis of the available evidence on the relative efficacy and safety of 2 drug-eluting stents (DES)—sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES)—in patients with coronary artery disease.

Background It is not known whether there are differences in late outcomes between the 2 most commonly used DES: SES and PES.

Methods Sixteen randomized trials of SES versus PES with a total number of 8,695 patients were included in this meta-analysis. A full set of individual outcome data from 5,562 patients was also available. Mean follow-up period ranged from 9 to 37 months. The primary efficacy end point was the need for reintervention (target lesion revascularization). The primary safety end point was stent thrombosis. Secondary end points were death and recurrent myocardial infarction (MI).

Results No significant heterogeneity was found across trials. Compared with PES, SES significantly reduced the risk of reintervention (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.63 to 0.87, $p < 0.001$) and stent thrombosis (HR 0.66; 95% CI 0.46 to 0.94, $p = 0.02$) without significantly impacting on the risk of death (HR 0.92; 95% CI 0.74 to 1.13, $p = 0.43$) or MI (HR 0.84; 95% CI 0.69 to 1.03, $p = 0.10$).

Conclusions Sirolimus-eluting stents are superior to PES in terms of a significant reduction of the risk of reintervention and stent thrombosis. The risk of death was not significantly different between the 2 DES, but there was a trend toward a higher risk of MI with PES, especially after the first year from the procedure. (J Am Coll Cardiol 2007; 50:1373–80) © 2007 by the American College of Cardiology Foundation

Drug-eluting stents (DES) have largely resolved the problem of restenosis, the major limitation of plain balloon angioplasty and bare-metal stenting (1). While several DES platforms have been evaluated in the setting of randomized studies and used in clinical practice, most of the accumulated evidence is related to sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) (2). These devices are the only DES approved by the U.S. Food and Drug Administration (3).

The DES have been linked to a higher risk of late stent thrombosis compared with bare-metal stents (4,5), a phenomenon that was not identified in the initial trials with short- to midterm follow-up (6). Furthermore, several studies suggested that SES and PES may be associated with increased mortality and myocardial infarction (MI) rates

See page 1381

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Abbreviations and Acronyms

CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)

(4,7–9). Serious concerns have been raised regarding the long-term safety of these DES (10–12), although more comprehensive, patient-based meta-analyses do not justify these concerns (13,14). The SES and PES differ importantly with respect to polymer coating and antiproliferative drugs, which may impact on the risk of late adverse events associated with these devices. Recently, the results of 2 meta-analyses suggested that the risk of late thrombosis or death might be different between SES and PES (4,9). However, the difference has been implied by indirect comparisons from trials comparing SES and PES with bare-metal stents separately (4,9). Thus, it remains uncertain whether there are any differences between SES and PES with regard to their long-term safety profile. Notwithstanding, a prior meta-analysis including 6 trials with 3,669 patients followed-up for up to 1 year has shown that SES are superior to PES in reducing the risk of restenosis (15). Whether the benefit of the SES is maintained beyond this period also remains unknown.

Direct comparison meta-analysis of randomized trials has the potential to increase power and improve precision of treatment effects (16). Availability of individual patient data is the "gold standard" to analyze time-to-event or survival data (17). Therefore, we performed a comprehensive meta-analysis with a large use of individual patient data from all clinical trials that have evaluated the long-term outcomes after coronary implantation of SES and PES.

Methods

Clinical trial selection. Randomized head-to-head trials of SES (Cypher, Cordis, Johnson & Johnson, Miami Lakes, Florida) and PES (TAXUS, Boston Scientific Corp, Natick, Massachusetts) in patients with coronary artery disease were identified through searches of the PubMed database, U.S. National Institute of Health, Cochrane Central Register of Controlled Trials, and the proceedings of the American Heart Association, American College of Cardiology, and European Society of Cardiology. Internet-based sources of information on the results of clinical trials in cardiology were also searched. Other data sources included reference lists of retrieved articles and pertinent reviews and editorials from leading medical journals. The last search was performed in April 2007.

Sixteen randomized clinical trials were included in this meta-analysis (18–33). The main characteristics of these trials are displayed in Table 1 and their definitions of events in Table 2.

Outcome variables. The primary efficacy end point of this meta-analysis was the need for reintervention (target lesion revascularization). The primary safety end point of this meta-analysis was stent thrombosis. Secondary end points were death and recurrent MI. All trials reported blind adjudication of adverse events made by the same events committee throughout the follow-up period. Event definitions for each trial are listed in Table 2.

Data collection and assessment of quality. Principal investigators or sponsors of each eligible trial were asked to complete electronic datasheets encompassing the following data for each individual patient: date of randomization; treatment assigned by randomization; death, MI, reintervention, stent thrombosis, and their respective date of occurrence; and date of last follow-up. Data for surviving patients were censored at the date of last contact. The principal investigators from 11 of the 16 randomized trials agreed to provide individual patient data (18,20,21,23–26,28–30,32). Summary outcome data of the remaining 5 trials were extracted from the respective publications or presentations or obtained directly from the investigators (19,22,27,31,33).

The following methodological criteria were evaluated for all included trials: adequacy of allocation concealment, performance of the analysis according to the intention-to-treat principle, and blind assessment of the outcomes of interest. No summary score was used to identify low or high quality trials; we did not perform weighting by quality scores as this practice has not been recommended by some (34–36).

Statistical analysis. Treatment effects, expressed as hazard ratios (HRs) or relative risks (for trials from which no individual patient data were available) for SES and PES, were first estimated for each trial and then combined using standard meta-analytic methods. Survival analyses were performed for each trial using the Mantel-Cox method, which is not based on the proportional hazards assumption; the log-rank test was used to calculate HRs with 95% confidence intervals (CIs). Trials in which the event of interest was not observed in any of the treatment groups were not included in the analysis of that event. For trials in which only one of the treatment groups had no events of interest, the treatment effect estimate and its standard error were approximated from 2×2 contingency tables after adding 0.5 to each cell (37). We used the Cochran test to assess heterogeneity across trials. Also, we calculated the I2 statistic to measure the consistency between trials with values of 25%, 50%, and 75% representing low, moderate, and high degrees of heterogeneity, respectively (38). The HRs from individual trials were pooled using both the fixed effects Mantel-Haenszel model (39) and the random effects DerSimonian and Laird model (40). If no heterogeneity is present, both models yield similar results. Herein, we report the results from the random-effects model. All p values are 2-sided. Statistical significance was assumed for $p < 0.05$. Statistical analysis was performed using the Stata software, version 9.2 (Stata Corp., College Station, Texas). Exploratory survival curves, which are presented as simple, non-stratified Kaplan-Meier curves across all trials, are con-

Table 1 Main Characteristics of the Trials Included in the Meta-Analysis

Study	No. of Patients	Mean Age (yrs)	Patient Profile	Primary End Point	Protocol-Mandated Follow-Up Angiography	Minimal Length of Thienopyridine Therapy in the SES/PES Groups (Months)	Mean Length of Follow-Up (Months)
BASKET (18)	545	64	Unselected patients	Cost-effectiveness based on the composite of death, MI, or reintervention	No	6/6	18
Cervinka et al. (19)	70	56	Complex lesions and patients	Neointima volume in intravascular ultrasound assessment	Yes	6/6	24
CORPAL (20)	652	61	Unselected patients	Angiographic restenosis and clinical events	Yes	12/12	31
Di Lorenzo et al. (21)	180	64	Acute MI	Death, MI, or reintervention	No	6/6	12
Han et al. (22)	416	NA	Multivessel disease	Death, MI, or reintervention	No	9/9	20
ISAR-DESIRE (23)	200	64	In-stent restenosis	Angiographic restenosis	Yes	6/6	34
ISAR-DIABETES (24)	250	68	Diabetic patients	Angiographic late loss	Yes	6/6	32
ISAR-SMART 3 (25)	360	67	Small vessels, nondiabetic patients	Angiographic late loss	Yes	6/6	34
LONG DES II (26)	500	61	Long lesions	Angiographic restenosis	Yes	6/6	13
Petronio et al. (27)	100	63	Complex lesions	Neointimal area in intravascular ultrasound assessment	Yes	6/6	36
PROSIT (28)	308	62	Acute MI	Cardiac death, reinfarction, stent thrombosis, or target lesion revascularization	Yes	6/6	26
REALITY (29)	1,353	63	Relatively unselected patients	Angiographic restenosis	Yes	2/6	24
SIRTAX (30)	1,012	62	Unselected patients	Death, MI, or reintervention	Yes	12/12	24
SORT OUT II (31)	2,098	64	Unselected patients	Death, MI, or reintervention	No	9/9	9
TAXI (32)	202	64	Unselected patients	Death, MI, or reintervention	No	12/12	37
Zhang et al. (33)	449	64	Unselected patients	Death, MI, or reintervention	No	9/12	12

BASKET = Basel Stent Kosten Effektivitäts Trial; CORPAL = Drug-Eluting Stents for Complex Lesions: Randomized Rapamycin Versus Paclitaxel trial; ISAR-DESIRE = Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis trial; ISAR-DIABETES = Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit From Paclitaxel-Eluting and Sirolimus-Eluting Stents trial; ISAR-SMART 3 = Drug-Eluting Stenting to Abrogate Restenosis in Small Arteries trial; LONG DES II = Randomized Comparison of the Efficacy of Sirolimus-Eluting Stent Versus Paclitaxel-Eluting Stent in the Treatment of Long Native Coronary Lesions trial; MI = myocardial infarction; PES = paclitaxel-eluting stent; PROSIT = Prospective Randomized Trial of Sirolimus- versus Paclitaxel-Eluting Stents for the Treatment of Acute ST-Elevation Myocardial Infarction; REALITY = Prospective, Randomized, Multi-Center Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems trial; SES = sirolimus-eluting stent; SIRTAX = Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization trial; SORT OUT II = Prospective, Multicenter, Large-Scale, Randomized Trial of Paclitaxel- and Sirolimus-Eluting Stents in "Real-World" Lesions trial; TAXI = Prospective Randomized Comparison Between Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology trial.

structed using S-Plus software version 4.5 (Insightful Corp., Seattle, Washington).

Results

A total of 16 randomized trials including 8,695 patients were analyzed (Table 1). The patients were representative of the whole clinical spectrum of coronary artery disease. Individual patient data were available from 11 trials including 5,562 patients who were followed up for a median of 24.3 months (25th, 75th percentiles: 18.4, 28.7 months) in the SES group and 24.3 months (25th, 75th percentiles: 18.3, 28.5 months) in the PES group ($p = 0.51$) (18,20,21,23–26,28–30,32).

Reintervention, the primary efficacy end point, was needed in 295 patients in the SES group versus 380 patients in the PES group. Allocation to the SES group was associated with a hazard ratio (HR) for reintervention of 0.74 (95% confidence interval [CI] 0.63 to 0.87, $p < 0.001$) (Fig. 1A). There was no significant heterogeneity across trials ($p = 0.39$). The sensitivity analysis yielded HRs that ranged from 0.69 (95% CI 0.59 to 0.82) to 0.78 (95% CI 0.66 to 0.92) and were not significantly different from the overall HR ($p \geq 0.58$). There was no significant interaction between the treatment effect and inclusion of follow-up angiography in the study protocol ($p = 0.10$). When the analysis was confined to the trials for which individual patient data were available, SES were associated with a HR for reintervention of 0.72 (95% CI 0.61 to 0.86, $p < 0.001$). Within the first year, the HR was 0.70 (95% CI 0.57 to 0.85, $p < 0.001$); after the first year, the HR was 0.79 (95% CI 0.58 to 1.09, $p = 0.15$). Figure 1B shows the probability curves of

JACC Vol. 50, No. 14, 2007
October 2, 2007:1373–80

Table 2 End Point Definitions in Each Trial Included in the Meta-Analysis

Study	MI	Reintervention	Stent Thrombosis
BASKET (18)	Typical chest pain with either typical rise of cardiac enzymes or new pathological Q waves/ST-T-wave changes on ECG	Intervention (PCI or CABG) driven by a lesion in the same epicardial vessel as initially treated	Angiographic evidence in the presence of an acute ischemic clinical event
Cervinka et al. (19)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥3 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Angiographic evidence
CORPAL (20)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥3 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Angiographic evidence
Di Lorenzo et al. (21)	Typical ECG changes and increase of CK-MB or troponin	Any CABG or PCI of the target vessel in the presence of symptoms or signs of ischemia	Angiographically documented thrombus within the stent associated to typical chest pain and ST-segment modification
Han et al. (22)	ECG changes and increase in cardiac enzymes	PCI due to angiographic restenosis	Angiographic evidence in the presence of an acute coronary syndrome
ISAR-DESIRE (23)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥3 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Angiographic evidence in the presence of an acute coronary syndrome
ISAR-DIABETES (24)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥3 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Angiographic evidence in the presence of an acute coronary syndrome
ISAR-SMART 3 (25)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥3 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Angiographic evidence in the presence of an acute coronary syndrome
LONG DES II (26)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥3 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia or only due to severe restenosis (≥70% diameter stenosis)	Angiographic evidence in the presence of an acute ischemic event
Petronio et al. (27)	ECG changes and increase in cardiac enzymes	PCI due to angiographic restenosis	Angiographic evidence in the presence of an acute coronary syndrome
PROSIT (28)	New electrocardiographic changes in association with a re-elevation of CK-MB	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia or only due to severe restenosis (≥70% diameter stenosis)	Angiographic documentation of stent occlusion with or without the presence of thrombus associated with an acute ischemic event, unexplained sudden death, or target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
REALITY (29)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥2 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia or only due to severe restenosis (≥70% diameter stenosis)	Early: a 30-day composite of death, Q-wave MI, or abrupt vessel closure requiring revascularization. Late: MI attributable to the target vessel with angiographic documentation of thrombus or total occlusion at the target site more than 30 days after the index procedure
SIRTAX (30)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥2 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia or only due to severe restenosis (≥70% diameter stenosis)	An acute coronary syndrome with angiographic documentation of either occlusion of the target lesion or thrombus within the previously stented segment
SORT OUT II (31)	ECG changes and increase in cardiac enzymes	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Definite: angiographically proven
TAXI (32)	Either pathological Q waves on ECG or an increase in cardiac enzymes ≥2 times the upper normal level	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Angiographic evidence
Zhang et al. (33)	ECG changes and increase in cardiac enzymes	PCI due to angiographic restenosis	Angiographic evidence in the presence of an acute coronary syndrome

CABG = aorto-coronary bypass surgery; CK-MB = creatine kinase-MB; ECG = electrocardiogram; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

reintervention: the 30-month probability of reintervention was 9.5% in the SES group and 12.7% in the PES group.

Stent thrombosis, the primary safety end point, was observed in 53 patients in the SES group versus 82 patients in the PES group. Allocation to the SES group was associated with a HR for stent thrombosis of 0.66 (95% CI 0.46 to 0.94, p = 0.02) (Fig. 2A). There was no significant heterogeneity across trials (p = 0.93). The sensitivity analysis yielded HRs that ranged from 0.55 (95% CI 0.36 to 0.84) to 0.75 (95% CI 0.51 to 1.09) and were not significantly different from the overall HR (p ≥ 0.52). When the analysis was confined to the trials

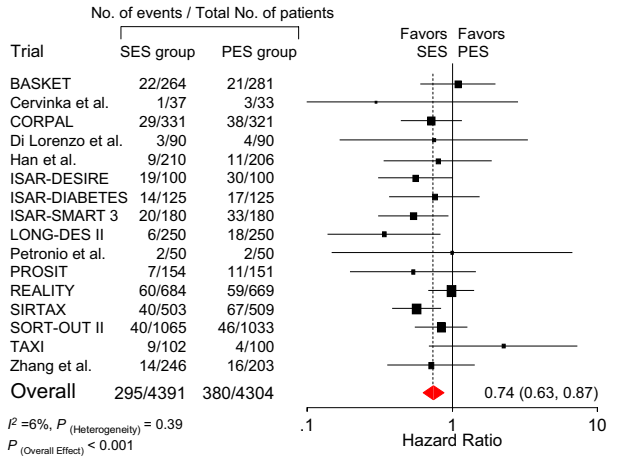

Figure 1 **Analysis of Reintervention According to the Drug-Eluting Stent Type**

(A) Absolute numbers of patients requiring reintervention and hazard ratios (HRs) for this end point with sirolimus-eluting stent (SES) versus paclitaxel-eluting stent (PES) for individual trials and pooled population. The HRs are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log HR. **(B)** Kaplan-Meier curves of reintervention in each of the stent groups for the pooled population. Hazard ratio indicates the HR associated with the SES. BASKET = Basel Stent Kosten Effektivitäts Trial; CI = confidence interval; CORPAL = Drug-Eluting Stents for Complex Lesions: Randomized Rapamycin Versus Paclitaxel trial; ISAR-DESIRE = Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis trial; ISAR-DIABETES = Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit From Paclitaxel-Eluting and Sirolimus-Eluting Stents trial; ISAR-SMART 3 = Drug-Eluting Stenting to Abrogate Restenosis in Small Arteries Trial; LONG DES II = Randomized Comparison of the Efficacy of Sirolimus-Eluting Stent Versus Paclitaxel-Eluting Stent in the Treatment of Long Native Coronary Lesions trial; PROSIT = Prospective Randomized Trial of Sirolimus- versus Paclitaxel-Eluting Stents for the Treatment of Acute ST-Elevation Myocardial Infarction; REALITY = Prospective, Randomized, Multi-Center Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems trial; SIRTAX = Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization trial; SORT OUT II = Prospective, Multicenter, Large-Scale, Randomized Trial of Paclitaxel- and Sirolimus-Eluting Stents in "Real-World" Lesions trial; TAXI = Prospective Randomized Comparison Between Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology trial.

for which individual patient data were available, SES were associated with a HR for stent thrombosis of 0.51 (95% CI 0.33 to 0.80, p = 0.003). Within the first year, the HR was 0.64 (95% CI 0.38 to 1.07, p = 0.09); after the first year, the HR was 0.30 (95% CI 0.12 to 0.72, p = 0.004). After the first year, 7 patients in the SES group and 21 patients in the PES group incurred stent thrombosis. Figure 2B shows the probability curves of stent thrombosis: the 30-month probability of stent thrombosis was 1.2% in the SES group and 2.6% in the PES group. As also shown by the curves, the difference was more evident after the first 12 months.

In the SES group, 169 patients died as compared with 173 patients in the PES group. Allocation to the SES group was associated with a HR for death of 0.92 (95% CI 0.74 to 1.13, p = 0.43) (Fig. 3A). There was no significant

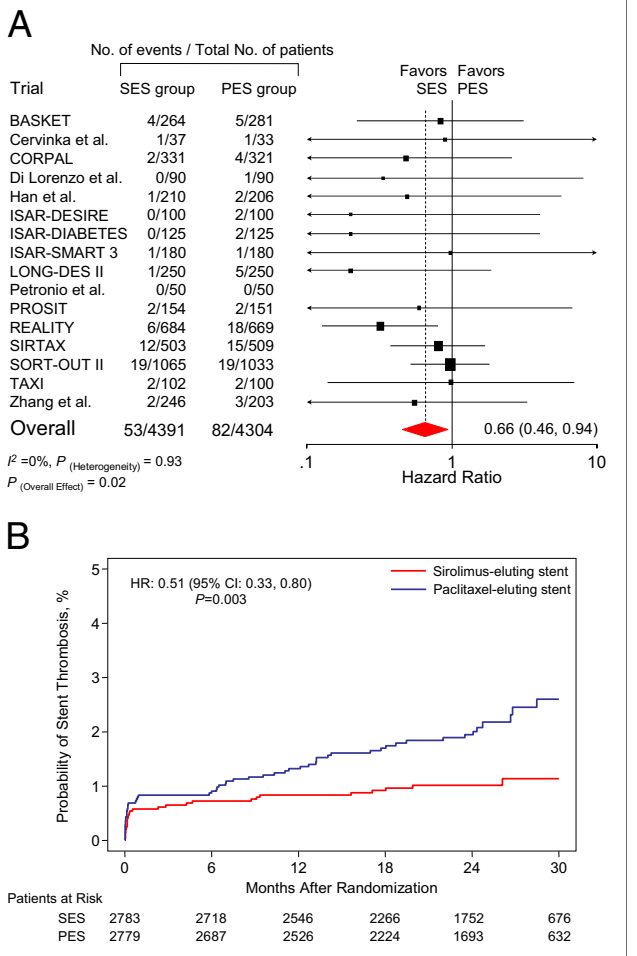

Figure 2 **Analysis of Stent Thrombosis According to the Drug-Eluting Stent Type**

(A) Absolute numbers of patients with stent thrombosis and HRs for stent thrombosis associated with SES versus PES for individual trials and pooled population. The HRs are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log HR. **(B)** Kaplan-Meier curves of stent thrombosis in the pooled population according to stent type. Abbreviations as in Figure 1.

JACC Vol. 50, No. 14, 2007
October 2, 2007:1373–80

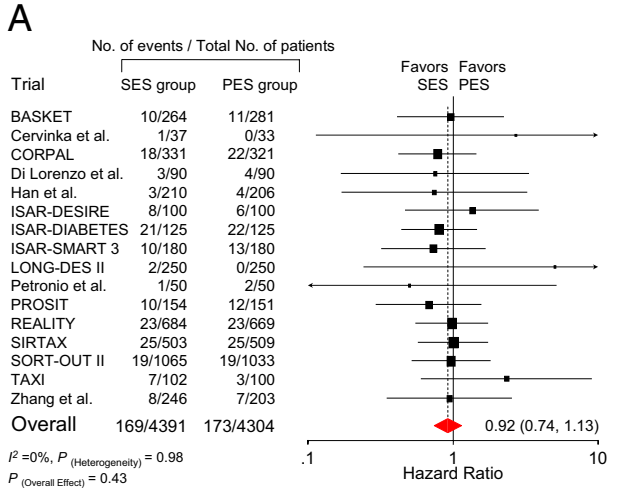

Figure 3 **Analysis of Mortality According to the Drug-Eluting Stent Type**

(A) Absolute numbers of patients experiencing death and HRs for death associated with SES versus PES for individual trials and pooled population. The HRs are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log HR. **(B)** Kaplan-Meier curves of mortality in each of the stent groups for the pooled population. Abbreviations as in Figure 1.

heterogeneity across trials (p = 0.98). The sensitivity analysis yielded HRs that ranged from 0.89 (95% CI 0.72 to 1.11) to 0.94 (95% CI 0.75 to 1.16) and were not significantly different from the overall HR (p ≥ 0.85). When the analysis was confined to the trials for which individual patient data were available, SES were associated with a HR for death of 0.92 (95% CI 0.73 to 1.17, p = 0.50). Within the first year, the HR was 1.02 (95% CI 0.73 to 1.45, p = 0.89); after the first year, the HR was 0.84 (95% CI 0.61 to 1.16, p = 0.29). Figure 3B shows the probability curves of death: the 30-month probability of death was 6.0% in the SES group and 6.3% in the PES group.

Myocardial infarction occurred in 178 patients in the SES group versus 205 patients in the PES group. Allocation to the SES group was associated with a HR for MI of 0.84 (95% CI 0.69 to 1.03, p = 0.10) (Fig. 4A). There was no significant heterogeneity across trials (p = 0.99). The sensitivity analysis yielded HRs that ranged from 0.80 (95% CI 0.64 to 0.99) to 0.87 (95% CI 0.69 to 1.10) and were not significantly different from the overall HR (p ≥ 0.74). When the analysis was confined to the trials for which individual patient data were available, SES were associated with a HR for MI of 0.81 (95% CI 0.64 to 1.02, p = 0.07). Within the first year, the HR was 0.91 (95% CI 0.71 to 1.17, p = 0.46); after the first year, the HR was 0.45 (95% CI 0.25 to 0.80, p = 0.006). After the first year, 18 patients in the SES group and 36 patients in the PES group incurred an MI. Figure 4B shows the probability curves of MI: the 30-month probability of MI was 5.3% in the SES group and 7.1% in the PES group. As also shown by the curves, the difference became more evident after the first 12 months.

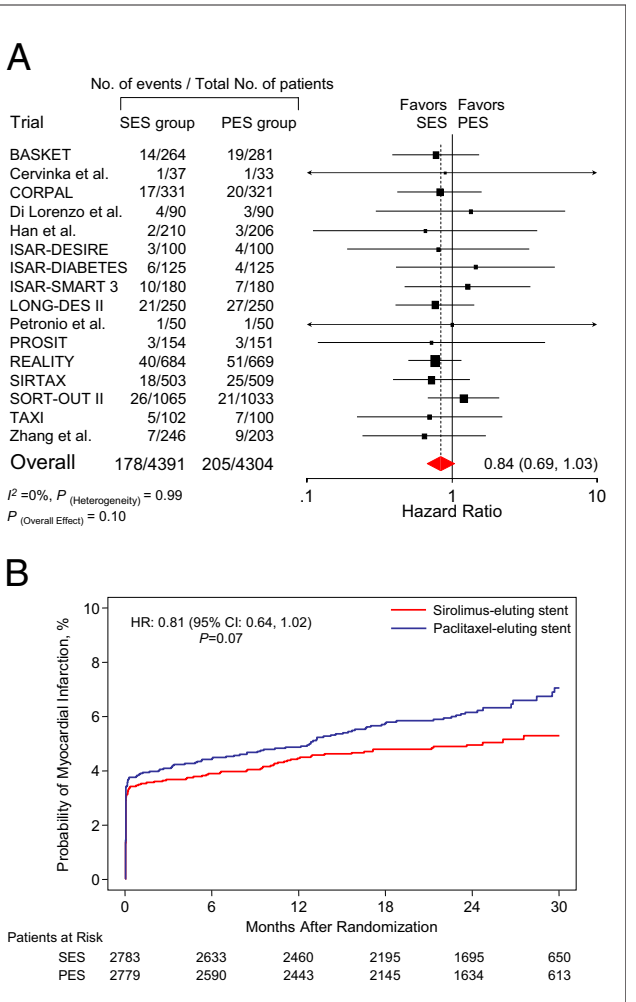

Figure 4 **Analysis of Myocardial Infarction According to the Drug-Eluting Stent Type**

(A) Absolute numbers of patients experiencing myocardial infarction associated with SES versus PES for individual trials and pooled population. The HRs are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log HR. **(B)** Kaplan-Meier curves of myocardial infarction in each of the stent groups for the pooled population. Abbreviations as in Figure 1.

Regarding the composite of death or MI, SES were associated with a HR of 0.86 (95% CI 0.72 to 1.01, p = 0.07).

Discussion

This meta-analysis compared long-term clinical outcomes after implantation of SES versus PES in a large population of patients with various clinical presentations of coronary artery disease. Compared with PES, SES significantly reduce the risk of reintervention and stent thrombosis without significantly impacting the risk of death or MI.

Three limitations should be acknowledged before commenting on the findings of this study. First, we were only able to obtain individual patient data from two-thirds of the trials. Completeness of patient-level data may increase the accuracy of the analysis. It is, however, reassuring that the treatment effects calculated for the entire population are in accordance with those obtained when individual patient data was analyzed. Second, 10 of the 16 trials included in this meta-analysis had a protocol-mandated follow-up angiography. This may exaggerate the risk of the occulostenotic reflex and lead to an increase in the number of reinterventions, although no significant interaction could be found between this study design feature and treatment effect. In addition, the fact that the difference in the risk of reintervention between the 2 DES types persisted even beyond the scheduled time for follow-up angiography (6 to 9 months) does not support a significant impact of protocol-mandated follow-up angiography on the treatment effect in favor of the SES observed in this meta-analysis. Third, all trials were open-label trials due to the impossibility of blinding completely different devices coming from 2 different manufacturers. Although all reported events went through a blind adjudication process, these limitations might have had an impact on the evaluation of at least 1 of the events of interest, the reintervention.

Sirolimus-eluting stents and PES are the most widely used drug-eluting stents to date. Delayed healing characterized by persistent fibrin deposition, poorer endothelialization, and local hypersensitivity reaction are some of the mechanisms put forward for the explanation of the late occurrence of thrombosis-related events with drug-eluting stents (41). There have been reports that these phenomena are more pronounced with PES than SES, at least in the presence of overlapping stents (42). We observed that patients treated with SES had a 34% reduction in the hazard of stent thrombosis relative to patients treated with PES. This finding, coupled with the fact that SES are associated with less late loss than PES (24,25,29,30), does not support the recently reported hypothesis that a greater late loss may have a protective role against stent thrombosis (12). Notably, the risk of both stent thrombosis and MI with PES was particularly higher after the first year. A different susceptibility to thrombosis after cessation of clopidogrel treatment between the 2 DES may explain the higher incidence of stent thrombosis with PES. A higher risk of late stent thrombosis with PES versus SES was also recently observed in a registry of a large series of patients (43). Although late stent thrombosis was numerically more frequent with PES, this complication was encountered with both DES types and requires maximal attention to improve long-term safety. These findings may indicate that patients who receive drug-eluting stents require a period of dual antiplatelet therapy longer than that currently recommended (44); this may be particularly important for patients who receive PES. We must acknowledge, however, 2 factors that may interfere with the results of the analysis of stent thrombosis. First, only recently there has been a strong interest in finding a common definition of stent thrombosis, which can be used universally in all drug-eluting stent trials. Although this would constitute an important step forward for future trials, the value of the retrospective application of new definitions for previously conducted trials is not proven. Second, although the recommended duration of clopidogrel therapy in each trial was known, we did not have information about the actual length of this therapy and related compliance for individual patients.

Conclusions

The SES are superior to PES in terms of a significant reduction of the risk of reintervention and stent thrombosis. The risk of death was not significantly different between the 2 DES, but there was a trend toward a higher risk of MI with PES, especially after the first year from the procedure.

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